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Anatomic Biomarkers of Macular Edema Associated with Retinal Vein Occlusion

Thomas A. Ciulla, MD, MBA[1], **Barry Kapik, MS**[1], **Allen Hu, MD**[2], **Alon Harris, MS, PhD**[3], **S. Michael, Ip, MD**[4], **Barbara Blodi, MD**[5]

[1]Clearside Biomedical, Alpharetta, Georgia.

[2]Cumberland Valley Retina Consultants, Hagerstown, Maryland.

[3]Icahn School of Medicine at Mount Sinai, New York City, New York.

[4]Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, California.

[5]Department of Ophthalmology, University of Wisconsin, Wisconsin, Madison.

Abstract

Purpose: To assess the relationship between best-corrected visual acuity (BCVA) and anatomic features in patients with macular edema (ME) related to retinal vein occlusion (RVO).

Design: Post hoc analysis of 3 clinical trials, which included verified diagnoses, protocol refractions, and the assessment of OCT and fluorescein angiography (FA) images at a masked reading center.

Participants: Patients diagnosed with RVO-ME.

Methods: Correlation analyses were performed to determine the correlation between BCVA and macular anatomy at baseline and at 12 and 24 weeks and between changes from baseline to 12 and 24 weeks.

Correspondence: Thomas A. Ciulla, MD, MBA, Clearside Biomedical, 900 North Point Parkway. Suite 200. Alpharetta, GA 30005 thomasciulla@gmail.com.

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Conception and design: Ciulla, Kapik
Data collection: Ciulla, Kapik, Blodi
Analysis and interpretation: Ciulla, Kapik, Hu, Harris, Ip, Blodi
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Overall responsibility: Ciulla, Kapik, Hu, Harris, Ip, Blodi

HUMAN SUBJECTS: Human subjects are included in this study. This post hoc study involved analysis of already-collected deidentified information from clinical trial protocols that were approved by an institutional review board or independent ethics committee at each study site.

These studies were performed in compliance with the provisions of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and the applicable local regulations.

Written informed consent was obtained from each patient before enrollment into the study using IRB-approved informed consent forms.

No animal subjects were used in this study.

Main Outcome Measures: The correlations between BCVA and central subfield thickness (CST), ellipsoid zone (EZ) integrity, intraretinal fluid (IRF), subretinal fluid, central leakage, and ischemia were assessed.

Results: In a total of 828 eyes with RVO-ME, the mean age, BCVA, and CST at baseline was 64.7 years, 51.1 letters, and 656.9 μm, respectively. At baseline, a moderate negative correlation was observed between BCVA and CST ($r = -0.56$, $P < 0.001$). At weeks 12 and 24, the mean BCVA of eyes with definitely abnormal (absent) EZ was statistically significantly worse than that of eyes with normal EZ. At week 12, a moderate negative correlation was observed between changes in BCVA and changes in CST ($r = -0.35$, $P < 0.001$), with a similar degree of association noted at week 24 ($r = -0.35$, $P < 0.001$). At weeks 12 and 24, eyes that showed any improvement in central IRF showed a greater improvement in BCVA than eyes that showed no improvement (week 12: 463 eyes, 18.3 letters vs. 177 eyes, 13.0 letters, respectively, $P < 0.001$) and (week 24: 332 eyes, 20.2 letters vs. 131 eyes, 13.3 letters, respectively, $P < 0.001$). With respect to the correlation between baseline BCVA and fluorescein leakage or capillary nonperfusion, the Pearson correlation coefficients were – 0.41 ($P < 0.001$) and – 0.16 ($P = 0.060$), respectively.

Conclusions: In addition to CST, there are important clinically relevant relationships between BCVA and both OCT and FA anatomic features in patients with RVO-ME.

Keywords

Central subfield thickness; Macular edema; Retinal vein occlusion; Visual acuity

In clinical practice, physicians often base treatment decisions on both best-corrected visual acuity (BCVA) and OCT assessments. Furthermore, findings such as central subfield thickness (CST) often represent an important secondary anatomic end point and a retreatment criterion in clinical trials for macular edema (ME) despite limited correlation between BCVA and CST.[1-8] Although there have been several large studies examining the relationship between BCVA and CST in patients with ME due to retinal vein occlusion (RVO),[3-7] there is limited literature on the comprehensive assessment of OCT and angiographic biomarkers in large patient populations.

The current study further assesses the relationship between BCVA and OCT and angiographic variables in patients with RVO-ME based on datasets from 1 phase II and 2 phase III clinical trials using monitor-verified diagnoses per eligibility criteria, protocol refractions, study-certified imagers, and spectral-domain OCT (SD-OCT) evaluation at a centralized masked reading center. These clinical trials assessed CLS-TA (Clearside Biomedical), an investigational formulation of the corticosteroid triamcinolone acetonide, for suprachoroidal (SC) injection. This report focuses on BCVA and anatomic correlations before administration of masked treatment and correlations between changes in BCVA and changes in anatomy, regardless of causality. Specifically, the relationships between BCVA and CST, the presence and location of intraretinal fluid (IRF) and subretinal fluid (SRF), the integrity of the ellipsoid zone (EZ; also known as the photoreceptor inner segment/outer segment junction), and angiographic leakage and ischemia were assessed. Correlation analyses were performed to describe the relationships at baseline and between changes from baseline to weeks 12 and 24.

Methods

Clinical Trials

This post hoc analysis was performed on datasets from 3 randomized controlled clinical trials, which assessed CLS-TA, wherein 4 mg (0.1 mL of 40 mg/mL) was administered suprachoroidally in conjunction with intravitreal (IVT) VEGF inhibitors in patients diagnosed with RVO-ME. This post hoc study involved an analysis of already-collected, deidentified information from clinical trial protocols that were approved by the institutional review board or an independent ethics committee at each study site, and these studies were performed in compliance with the provisions of the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and the applicable local regulations. Written informed consent was obtained from each patient before enrollment into the study using institutional review board-approved informed consent forms.

The study designs are summarized below. The key eligibility features are summarized in Table 1. Throughout this article, the term "patient" has been used instead of "eye" because dosing was performed unilaterally, i.e., in the study eye, in all the studies. [1]

1. SAPPHIRE ("A Randomized, Masked, Controlled Trial to Study the Safety and Efficacy of Suprachoroidal CLS-TA in Conjunction with Intravitreal Aflibercept in Subjects with Retinal Vein Occlusion"; ClinicalTrials.gov identifier, NCT02980874) was a phase III randomized, masked, active-controlled, parallel-group, multicenter study in treatment-naïve patients with ME secondary to RVO, a CST of > 300 μm, and a BCVA score between 20 and 70 letters, inclusively, in the study eye. The study was designed to compare the efficacy and safety of suprachoroidally injected CLS-TA (4 mg/100 mL, standard dose across trials), which was administered in conjunction with IVT aflibercept (2 mg/50 mL; active group), versus that in a control group, in which IVT aflibercept was administered in conjunction with a sham SC procedure (involving pressing the hub of a needleless syringe against the globe of the eye to simulate the injection of the study medication) over 48 weeks of follow-up. Four hundred sixty patients were enrolled and randomly assigned in a ratio of 1:1 to 1 of 2 treatment groups stratified by disease (branch retinal vein occlusion [BRVO] or central retinal vein occlusion [CRVO]). Two hundred thirty-one patients were assigned to the active arm, and 229 patients were assigned to the control arm. The safety and efficacy outcomes, including BCVA and OCT, were assessed at baseline, monthly for 24 weeks, and then every 6 weeks until the end of the study at week 48. Fluorescein angiography (FA) was performed at baseline and at weeks 24 and 48. The patients in the active arm received IVT aflibercept and SC CLS-TA on day 0 (baseline) and at weeks 12 and 24; IVT aflibercept monotherapy at week 4; and sham IVT aflibercept at weeks 8, 16, and 20. The patients in the control arm received IVT aflibercept and sham SC administration on day 0 and at weeks 12 and 24 and IVT aflibercept monotherapy at weeks 4, 8, 16, and 20. All patients were eligible for rescue at other visits, as determined based on predefined criteria.

This superiority trial was considered to have failed because the active arm was not statistically different from the control arm (i.e., neither statistically worse nor better) at 8 weeks (primary efficacy end point) and was terminated. However, 255 patients (55.4%) completed the study before termination.

2. TOPAZ ("A Randomized, Masked, Controlled Trial to Study the Safety and Efficacy of Suprachoroidal CLS-TA with an Intravitreal Anti-VEGF in Subjects with Retinal Vein Occlusion"; ClinicalTrials.gov identifier, NCT03203447), initiated 9 months after SAPPHIRE, was identical in design and had the same goals as SAPPHIRE, except for the anti-VEGF agent used (randomized to either bevacizumab [1.25 mg/50 mL intravitreally] or ranibizumab [0.5 mg/50 mL intravitreally] instead of aflibercept). Four hundred sixty patients were to be enrolled and assigned randomly in a ratio of 1:1:1:1 to 1 of 4 treatment groups stratified by disease (BRVO or CRVO). However, because of the failure of SAPPHIRE to meet its primary efficacy end point, TOPAZ was terminated after randomizing 325 patients (active arm, 162 patients; control arm, 163 patients) and before any patient completed the study.

3. TANZANITE ("Safety and Efficacy of Suprachoroidal CLS-TA in Combination with Intravitreal Aflibercept in Subjects with Macular Edema Following Retinal Vein Occlusion"; ClinicalTrials.gov identifier, NCT02303184) was a phase II, multicenter, randomized, active-controlled, masked, parallel-arm study of treatment-naïve patients with ME secondary to RVO that evaluated the effect of a single dose of CLS-TA administered suprachoroidally in conjunction with IVT aflibercept compared with that of IVT aflibercept plus a sham SC procedure over 12 weeks of follow-up. The safety and efficacy outcomes were assessed at baseline and then monthly for 12 weeks. The study enrolled 46 patients with RVO randomized in a ratio of 1:1 to each of the 2 arms. All 46 patients completed the study and were included in all the analyses. The study details are further summarized in Table 1 and the study by Campochiaro et al.[9]

SD-OCT

The CST and the presence and location of IRF and SRF, relative to the central subfield, were assessed using SD-OCT. The central subfield is a circular area of 1-mm diameter centered around the center point. For each scan, the standard 9-field ETDRS grid was centered at the fovea by viewing all B-scans to locate foveal landmarks, which included the point at which the inner retinal layers were the thinnest, and the foveal depression or hyper-reflective dot that corresponded to reflected light at the foveal center. These landmarks are helpful in locating the center point, particularly in the presence of ME. No instrument-specific upper limits for CST, IRF, or SRF were used for study enrollment because the eligibility criteria across the clinical trials did not include an upper limit. The IRF and SRF were graded as absent, questionable, definitely outside the central subfield, definite central subfield involvement, and ungradable.

The SD-OCT instrument and technician were certified before screening any patients. The research sites were encouraged to use the same technician and equipment throughout the

patient's participation in the study. Deidentified images were uploaded to Merit (formerly Eyekor) CRO grading platform for image and data management. Images were graded by trained and qualified evaluators at the Wisconsin Reading Center.

Across all 3 studies, OCT images were taken at baseline and at every visit thereafter for the entire duration of the study.

FA

Fluorescein angiography was used to assess fluorescein leakage and capillary nonperfusion within the ETDRS grid. Fluorescein leakage is related to a pathophysiology that leads to ME and is a complementary end point of CST for analysis. The area of capillary nonperfusion is related to visual prognosis in patients with RVO and is useful for the analysis of risk factors.

The FA equipment and photographers were certified before screening any study patients. As with SD-OCT, the sites were encouraged to use the same technician and equipment throughout the patient' s participation in the study. Deidentified images were uploaded to the Merit (formerly Eyekor) CRO grading platform for image and data management. Images were graded by trained and qualified evaluators at the Wisconsin Reading Center.

In TANZANITE, FA was performed at baseline and every 4 weeks for 12 weeks. In the 2 phase III trials, FA examinations were performed at baseline and at weeks 24 and 48.

EZ Integrity

Prospective grading of EZ integrity was not planned for the 3 clinical trials. The integrity of EZ in a randomly selected subset of patients from SAPPHIRE was graded post hoc by trained and qualified evaluators from Wisconsin Reading Center based on deidentified images obtained from Merit (formerly Eyekor) CRO. Approximately 75 patients per treatment arm were randomly selected based on the availability of complete data, i.e., nonmissing BCVA and CST data at baseline and at weeks 12 and 24. A total of 150 eyes were chosen for the analysis because this value represented > 50% of completers and because similar sample sizes were sufficient for similar EZ analyses in previously published studies.[4,10] The integrity of the central EZ was graded as normal, questionably abnormal, definitely abnormal (patchy), definitely abnormal (absent), and ungradable.

BCVA Assessment

The BCVA was evaluated with the ETDRS visual acuity chart using standardized lighting and standardized lanes. The results were reported as the total number of letters read after protocol refraction. Visual acuity testing preceded any examination requiring contact with the eye. To provide standardization and well-controlled assessments of BCVA during the study, all BCVA assessments were performed by trained staff who were masked to treatment and were certified on the study procedure using certified visual acuity equipment or lanes.

Across all 3 studies, the assessment of BCVA was performed at baseline and at every visit thereafter for the entire duration of the study.

Correlation Analyses

This post hoc analysis was performed using data from 3 randomized controlled clinical trials: SAPPHIRE, TOPAZ, and TANZANITE. All patients in these studies received ≥ 1 treatments with SC CLS-TA, which was administered in conjunction with an IVT anti-VEGF agent or an IVT anti-VEGF agent plus a sham SC procedure using a syringe with a needleless hub. Because the purpose of this analysis was to assess the correlations between BCVA and both OCT and FA anatomic features and not to assess the effectiveness of treatment, data from all patients were included, regardless of treatment assignment or compliance or the administration of rescue therapy.

Pooled data from all 3 studies were analyzed. Correlation analyses were performed on baseline data collected before dose administration and separately on changes from baseline to weeks 12 and 24. Only patients with complete data, i.e., BCVA and OCT or FA anatomic features assessed on the same date, were included in the analysis. Additionally, patients with missing baseline BCVA or CST were excluded from the analysis.

As previously noted, EZ integrity and the presence and location of IRF and SRF were each graded into 4 levels of severity, in addition to those that were ungradable. Values that were ungradable were excluded from these analyses, and values for missing data were not imputed.

To investigate the impact of RVO subtype on the relationships between BCVA and other OCT biomarkers, separate analyses were performed on patients diagnosed with BRVO and patients diagnosed with CRVO.

Unless otherwise stated, reported *P* values were not adjusted for multiplicity, and statistical significance was reported using a false-positive rate of 0.050. All tests were conducted using 2-sided alternatives. Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc).

CST

To measure the linear relationships between baseline BCVA and CST, between change in BCVA from baseline and baseline CST, and between change from baseline in BCVA and CST, the Pearson correlation coefficients, 95% confidence intervals (CIs) using Fisher *z* transformation, and *P* values based on the 2-sided test for zero linear correlation were calculated. To describe the relationship between baseline BCVA and CST, a multiple linear regression model was used with BCVA as the dependent variable and CST and age as independent variables. To describe the relationship between change in BCVA from baseline to weeks 12 and 24 and baseline CST, a multiple linear regression model was used with change in BCVA from baseline as the dependent variable and baseline CST, baseline BCVA, and age as independent variables. To describe the relationship between changes in BCVA and CST from baseline, a multiple linear regression model was used with change in BCVA from baseline as the dependent variable and change in CST from baseline, baseline BCVA, baseline CST, and age as independent variables. To assess the fitness of these multiple linear regression models, simple linear regression models containing CST as the independent variable were used.

IRF and SRF

Using the pooled data, the relationships between baseline BCVA and baseline IRF and SRF were assessed using an analysis of covariance model with baseline OCT anatomy as the independent variable and baseline CST and age as covariates. The mean BCVA values were compared across the anatomic grades. To assess the fitness of this model, the analysis of variance was performed without the covariates. The Tukey–Kramer multiple-comparison procedure was used to account for multiplicity issues related to multiple testing within each anatomic feature.

To assess the relationships between baseline IRF and SRF and changes in BCVA at 12 and 24 weeks, an analysis of covariance model was used with change in BCVA from baseline as the dependent variable and baseline anatomy (categorized as either “center not involved” or “center involved”) as the independent variable, with baseline BCVA, baseline CST, and age as covariates. To assess the fitness of this model, the analysis of variance was performed without the covariates.

The relationship between change in BCVA from baseline and change in the anatomic status at weeks 12 and 24 was assessed using an analysis of covariance model with anatomic status (categorized as either “any improvement” or “no improvement or worsening”) as the independent variable and age, baseline BCVA, and baseline CST as covariates. The fitness of these models was compared with that of analogous analysis of variance models without the addition of covariates.

Capillary Nonperfusion and Fluorescein Leakage

To measure the linear relationships between baseline BCVA and FA anatomy (fluorescein leakage and capillary nonperfusion), between change in BCVA from baseline and baseline FA anatomy, and between change in BCVA from baseline and FA anatomy, the Pearson correlation coefficients, 95% CIs using Fisher z transformation, and P values based on the 2-sided test for zero linear correlation were calculated. To describe the relationship between baseline BCVA and FA anatomy, a multiple linear regression model was used with BCVA as the dependent variable and FA anatomy, baseline CST, and age as independent variables. To describe the relationship between change in BCVA from baseline to week 24 and baseline FA anatomy, a multiple linear regression model was used with change in BCVA from baseline as the dependent variable and baseline FA anatomy, baseline BCVA, baseline CST, and age as independent variables. To describe the relationship between change in BCVA from baseline to week 24 and FA anatomy, a multiple linear regression model was used with change in BCVA from baseline as the dependent variable and change in FA anatomy from baseline, baseline BCVA, baseline CST, and age as independent variables. To assess the fitness of these multiple linear regression models, simple linear regression models containing FA anatomy as the independent variable were used.

EZ Integrity

The analysis of the integrity of EZ in the random sample of patients in SAPPHIRE was initially planned to mirror those planned for IRF and SRF, but nearly all patients in the sample had a baseline EZ grade of being ungradable because of the presence of significant

SRF or large cysts, rendering baseline EZ unevaluable. Consequently, the relationship between BCVA and EZ integrity at weeks 12 and 24 were assessed separately using an analysis of covariance model with BCVA as the dependent variable and EZ integrity as the independent variable, with baseline CST and age as covariates. The Tukey–Kramer multiple-comparison procedure was used to account for multiplicity issues related to multiple testing.

Results

The data on demographic and baseline characteristics are summarized in Table 2. A total of 828 eyes from 828 patients contributed BCVA and anatomy data to this analysis, with all eyes diagnosed with RVO-ME. The demographic, baseline, and disease characteristics were well balanced between the 3 studies. The mean age, BCVA, and CST at baseline for the entire population was 64.7 years, 51.1 letters, and 656.9 μm, respectively. Nearly half of the patients (45.5%) were women, and most patients (80.8%) still retained their natural lens in the study eye at study entry. The patients were diagnosed with BRVO (54.7%), CRVO (45.2%), or hemiretinal vein occlusion (0.1%) at an overall average duration of 33.0 days. Overall, there were no meaningful differences in the relationships between OCT anatomic biomarkers and BCVA, based on the type of RVO. Consequently, presented herein are analyses of eyes, irrespective of the type of RVO (Table 3, 4, 5, 6 and 7), except for the analysis of correlation between BCVA and CST (Table 3), given its largest sample size.

Association between BCVA and OCT or FA Anatomic Features at Baseline

The analysis of baseline BCVA and OCT data included 828 eyes with gradable images for CST. A moderate negative correlation was observed between BCVA and CST ($r = -0.56$, $P < 0.001$). The slope of the linear regression line reflected an average increase of 3.28 letters in BCVA (95% CI, 2.96–3.61 letters) for every 100-μm reduction in CST, as shown in Table 3. At baseline, CST accounted for 31.66% of the total variation in BCVA. When age was included in the multiple regression model, this value increased to 33.21%, as shown in Table 8.

The analysis of the association between baseline BCVA and IRF included data from 812 eyes with gradable OCT images. Of these, most eyes (96%) had definite centrally involved IRF. The mean BCVA at baseline ranged from a high value in eyes with questionable IRF (55.0 letters) to a low value in eyes without IRF (42.2 letters). None of the differences in the mean BCVA between the 4 grades were statistically significant, as seen in Table 4. Intraretinal fluid accounted for 0.60% of the variation observed in BCVA at baseline. This value rose to 33.62% when baseline CST and age were added as covariates to the model, as shown in Table 8.

Most of the eyes (60%) with OCT images gradable by the reading center (n = 744) showed definite centrally involved SRF at baseline. The mean BCVA at baseline ranged from a high value of 54.9 letters in eyes with definite centrally involved SRF to a low value of 41.1 letters in eyes with definite SRF located outside of the central subfield. The differences in mean BCVA between eyes with definite centrally involved SRF and eyes with lesser degrees of SRF were statistically significant ($P < 0.001$) after adjusting for multiple comparisons, as seen in Table 5. Subretinal fluid accounted for 3.00% of the total variation in baseline

BCVA. When baseline CST and age were included as covariates in the model, it rose to 31.32%, as shown in Table 8.

At baseline, a total of 578 eyes had FA images that were gradable for fluorescein leakage by the reading center. A moderate negative correlation was observed between BCVA and the area of fluorescein leakage within the ETDRS grid ($r = -0.41$, $P < 0.001$). The slope of the regression line reflected an average increase of 1.98 letters in BCVA (95% CI, 0.93–3.03 letters) for every 10-mm^2 reduction in the area of fluorescein leakage, as shown in Table 6. At baseline, the area of fluorescein leakage accounted for 16.76% of the total variation in BCVA. When baseline CST and age were included in the multiple linear regression model, this value rose to 34.53%, as shown in Table 8.

The analysis of the correlation between BCVA and the area of capillary nonperfusion within the ETDRS grid at baseline included 135 eyes with gradable FA images. A small and statistically insignificant negative correlation was observed ($r = -0.16$, $P = 0.060$). The slope of the linear regression line reflected an average increase of 2.87 letters in baseline BCVA (95% CI, – 1.48 to 7.22 letters) for every 10-mm^2 reduction in the area of capillary nonperfusion, as shown in Table 6. The area of capillary nonperfusion accounted for 2.64% of the variation in BCVA at baseline; this value rose to 39.31% when baseline CST and age were added as covariates to the multiple regression model, as shown in Table 8.

When stratified by RVO subtype, the analysis of baseline BCVA and CST showed a moderate negative correlation in both patients with BRVO (n = 453 eyes; $r = -0.42$, $P < 0.001$) and those with CRVO (n – 374 eyes; $r = -0.59$, $P < 0.001$). The slope of the linear regression lines reflected an average increase of 2.75 letters in BCVA (95% CI, 2.21–3.29 letters) for every 100-μm reduction in CST in eyes with BRVO and an average increase of 3.56 letters in BCVA (95% CI, 3.08–4.03 letters) for every 100-μm reduction in CST in eyes with CRVO, as shown in Table 3.

Figure 1 shows the relationships between these anatomic outcomes and BCVA at baseline.

Association between Changes in BCVA at 12 and 24 Weeks and Baseline OCT or FA Anatomic Features

The analysis of change in BCVA from baseline and baseline CST included data from 632 eyes at week 12 and 455 eyes at week 24 with gradable images for CST. A moderate positive correlation was observed between BCVA change at week 12 and baseline CST ($r = 0.31$, $P < 0.001$), with a similar degree of association noted between BCVA change at week 24 and baseline CST ($r = 0.25$, $P < 0.001$). The slope of the linear regression line reflected an average decrease of 0.31 letters in BCVA (95% CI, – 0.73 to 0.11 letters) at week 12 for every 100-μm in baseline CST and an average increase of 0.20 letters in BCVA at week 24 (95% CI, – 0.36 to 0.76 letters) for every 100 μm in baseline CST, as shown in Table 3.

The analysis of change in BCVA from baseline and baseline IRF included data from 575 eyes at week 12 and 433 eyes at week 24. Eyes with centrally involved IRF at baseline did not show significantly more improvement in BCVA than those without center involvement

at week 12 (17.1 vs. 15.5 letters, respectively; $P = 0.563$) or week 24 (18.6 vs. 14.4 letters, respectively; $P = 0.188$), as shown in Table 4.

The analysis of change in BCVA from baseline and baseline SRF included data from 527 eyes and 388 eyes at weeks 12 and 24, respectively. The mean improvement in BCVA in eyes with centrally involved SRF at baseline was not significantly different from those eyes without centrally involved SRF at baseline at week 12 (16.9 vs. 15.8 letters, respectively; $P = 0.250$) or week 24 (18.2 vs. 17.1 letters, respectively; $P = 0.421$), as shown in Table 5.

The analysis of the correlation between change in BCVA from baseline and baseline area of fluorescein leakage included 190 eyes at week 24, comprised entirely of patients from SAPPHIRE and TOPAZ with gradable FA images. At week 24, a minor negative linear correlation that was not statistically significant was observed between change in BCVA from baseline and baseline area of fluorescein leakage ($r = -0.06$; $P - 0.384$), as shown in Table 6.

The analysis of the correlation between change in BCVA from baseline and baseline capillary nonperfusion included 39 eyes at week 24 that were gradable by the reading center. There was no significant association between baseline capillary nonperfusion and change in BCVA from baseline at week 24, but the analysis was limited by sample size, as shown in Table 6.

The results of the analysis of the correlation between change in BCVA from baseline and baseline CST, when evaluated by RVO subtype, were not dissimilar from the results for the whole population, as shown in Table 3.

Figure 2 shows the relationships between these anatomic outcomes at baseline and change in BCVA from baseline at week 24.

Association between Changes in BCVA and Changes in OCT or FA Anatomic Features at 12 and 24 Weeks

The analysis of change in BCVA from baseline and change in OCT from baseline data included 632 eyes at week 12 and 455 eyes at week 24 with gradable images for CST. At week 12, a moderate negative correlation was observed between changes in BCVA and changes in CST ($r = -0.35$, $P < 0.001$), with a similar degree of association noted at week 24 ($r = -0.35$, $P < 0.001$). The slope of the linear regression line at week 12 reflected an average increase of 2.45 letters in BCVA (95% CI, 1.56–3.35 letters) for every 100-μm reduction in CST and an average increase of 2.87 letters in BCVA at week 24 (95% CI, 1.89–3.84 letters), as shown in Table 3. At week 24, the change in CST from baseline accounted for 12.25% of the total variation in BCVA. When baseline BCVA, CST, and age were included in the multiple regression model, this value rose to 30.07%, as shown in Table 8.

At weeks 12 and 24, eyes that showed any improvement in central IRF showed greater improvement in BCVA than eyes that showed no improvement or worsened (week 12: 463 eyes, 18.3 letters vs. 177 eyes, 13.0 letters, respectively, $P < 0.001$) and (week 24: 332 eyes, 20.2 letters vs. 131 eyes, 13.3 letters, respectively, $P < 0.001$), as shown in Table 4. The

change in IRF from baseline accounted for 3.90% of the variation observed in the change in BCVA from baseline at week 24. This value rose to 29.70% when baseline BCVA, CST, and age were included as covariates in the analysis of variance model, as shown in Table 8.

With regard to SRF, there were no clinically meaningful or statistically significant differences between eyes that showed any improvement and eyes that showed no improvement or worsened at weeks 12 and 24, as shown in Table 5. The change in SRF from baseline accounted for 0.03% of the variation observed in the change in BCVA from baseline at week 24. This value rose to 25.34% when baseline BCVA, CST, and age were added as covariates to the model, as shown in Table 8.

The analysis of the correlation between change in BCVA from baseline and the area of fluorescein leakage included 190 eyes at week 24, comprised entirely of patients from SAPPHIRE and TOPAZ with gradable FA images. At week 24, there was a minor negative linear relationship that was not significant ($r = -0.07$; $P = 0.323$), as shown in Table 6. The change in the area of fluorescein leakage from baseline at week 24 accounted for 0.50% of the total variation in the change in BCVA from baseline at week 24. The addition of baseline BCVA, CST, and age to the linear regression model resulted in this value rising to 27.82%, as shown in Table 8.

At week 24, a total of 39 eyes had FA images that were gradable for the area of capillary nonperfusion by the reading center. There was no significant association between capillary nonperfusion and BCVA, but the analysis was limited by sample size, as shown in Table 6. At week 24, the area of capillary nonperfusion accounted for 2.76% of the total variation in the change in BCVA from baseline. When baseline BCVA, CST, and age were included in the multiple linear regression model, this value rose to 46.60%, as shown in Table 8.

The results of the analysis of the correlation between change in BCVA from baseline and CST, when evaluated by RVO subtype, were similar to the results shown for the whole population, as shown in Table 3.

Figure 3 shows the relationships between changes in these anatomic outcomes from baseline and change in BCVA from baseline at week 24.

Association between BCVA and EZ Integrity at Weeks 12 and 24

As noted earlier, nearly all patients had ungradable baseline EZ because of the presence of significant SRF or large cysts, rendering baseline EZ unevaluable. Consequently, the relationship between BCVA and EZ integrity was not assessed at baseline, and only assessed at weeks 12 and 24.

The analysis of BCVA and EZ integrity included data from 145 eyes at week 12 and 142 eyes at week 24 with gradable images. At week 12, the mean BCVA ranged from a high value of 74.4 letters in eyes with normal EZ integrity and progressively decreased to a nadir of 58.0 letters in eyes with definitely abnormal (absent) EZ. The differences in mean BCVA between eyes with definitely abnormal (absent) EZ and each of the other 3 groups were statistically significant ($P \leq 0.005$) after adjusting for multiple comparisons, as seen in Table 7. Similarly, at week 24, the mean BCVA ranged from a high value of 77.6 letters in eyes

with normal EZ integrity to a low value of 60.6 letters in eyes with definitely abnormal (absent) EZ. The differences in mean BCVA between eyes with definitely abnormal (absent) EZ and eyes with normal and definitely abnormal (patchy) EZ were statistically significant ($P \leq 0.001$), as seen in Table 7.

The relationship between BCVA and EZ integrity at weeks 12 and 24 is shown in Figure 4.

Discussion

This study assessed the relationship between BCVA and OCT and angiographic features in patients with RVO-ME. A few previous large studies have comprehensively examined the correlations between BCVA and OCT or angiography-determined anatomic features in patients with RVO-ME. One post hoc analysis assessed the relationship between BCVA and CST in 387 patients from 6 prospective clinical trials (4 single-center and 2 multicenter studies) of anti-VEGF treatment for neovascular age-related macular degeneration, diabetic macular edema, and RVO.[3] In patients with RVO-related ME, baseline BCVA was not correlated with baseline CST, but the authors noted that these RVO studies had enrolled ischemic cases, which highlights the inability of CST to reflect ischemia-related changes in BCVA. However, the correlation between changes in BCVA and changes in CST did show a moderate negative correlation in patients with diabetic macular edema ($r = -0.45$) and RVO ($r = -0.35$) at 12 months, similar to the correlation in changes at 24 weeks in the current study. In the Standard Care versus COrticosteroid for REtinal Vein Occlusion study, which included 271 patients with CRVO-related ME, the correlation between baseline BCVA and central point thickness showed a low-to-moderate negative correlation[5]; the correlation between changes in BCVA and changes in central point thickness at 4 and 12 months showed low-to-moderate negative correlation.[6] In the Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA study, which assessed a dexamethasone implant in patients with CRVO- and BRVO-related ME, the correlation between changes in BCVA and changes in CST at 6 months also showed a low-to-moderate negative correlation in 403 patients who received 0.7 mg of the implant ($r = -0.34$), nearly identical to the current study.[7]

Another study involving patients from the same phase III trials (but not including patients from the phase II TANZANITE trial) as the current analysis similarly reported a moderate negative correlation between BCVA and CST ($r = -0.56$) at baseline, with CST accounting for only 32% of the total variation in BCVA.[4] Similarly, there was a moderate negative correlation between the changes in the values from baseline to 24 weeks ($r = -0.35$), with change in CST accounting for only 12% of the total variation in the change in BCVA.[4] Acute and chronic ME showed similar correlations.[4]

The current study further expands on anatomic biomarkers of RVO-ME, beyond CST, specifically assessing the associations of BCVA with EZ integrity and the presence and location of IRF or SRF as well as the associations between BCVA and angiographic biomarkers. At baseline, 96% and 60% of the eyes showed the central subfield definitely involved with IRF and SRF, respectively. Eyes with centrally involved IRF or SRF

at baseline did not show significantly worse vision than eyes with a lesser degree of involvement.

With respect to changes in anatomy and visual function, eyes that showed any improvement in central IRF showed a greater improvement in BCVA than eyes that showed no improvement or worsened at both weeks 12 and 24. However, with regard to SRF, there were no clinically meaningful or statistically significant differences between eyes that showed any improvement and eyes that showed no improvement or worsened at weeks 12 and 24.

With respect to angiographic biomarkers, there was a moderate negative and low negative correlation between baseline BCVA and leakage and between baseline BCVA and ischemia, respectively, but neither was statistically significant. Importantly, the visual acuity inclusion criteria in this study likely limited the number of patients with ischemia and the range of ischemia. Nevertheless, in the combined model, baseline CST, IRF, SRF, leakage, ischemia, and age could account for nearly 50% of the variation in baseline BCVA (Table 8). The correlation between changes in BCVA and changes in leakage at week 24 remained low and insignificant. In the combined model, the aforementioned parameters could account for nearly 28% of the variation in the change in BCVA at week 24 (Table 8).

For EZ, at weeks 12 and 24, the mean BCVA of eyes with definitely abnormal (absent) EZ was statistically significantly worse than that of eyes with normal EZ. These findings are consistent with previous studies, in which EZ showed functional correlation in patients with ME due to RVO, diabetic macular edema, and noninfectious uveitis.[10-17]

A limitation of this analysis is its post hoc design. Another limitation is the difference in the study designs of the phase II and III trials. TANZANITE collected only FA images at baseline and at week 12, whereas SAPPHIRE and TOPAZ collected only FA images at baseline and at weeks 24 and 48. As a result of this limitation and its effect on the availability of gradable images at week 12, the FA analyses were limited to data from baseline and from week 24. Therefore, baseline is the only time point at which the FA data from all 3 studies were pooled. In addition, a limitation of the grading of the central subfield anatomic features (EZ, IRF, and SRF) into discrete categories may lead to low sensitivity to changes in anatomy. Further, with regard to EZ, nearly all patients had a baseline grade of being ungradable because of the presence of significant SRF or large cysts, rendering baseline EZ unevaluable and limiting the analysis to 12 and 24 weeks. These grading issues, protocol differences, and early termination of SAPPHIRE and TOPAZ decreased the sample sizes of some of the analyses, representing another limitation of this study. In addition, this study did not assess other OCT biomarkers, such as disorganization of retinal inner layers, which also shows some functional correlation in patients with these disorders. Finally, the results of this study cannot be extrapolated to all patients receiving all treatments for RVO-ME. However, the strength of this analysis includes the use of clinical trial data, which involved monitor-verified diagnoses per eligibility criteria, protocol refraction, study-certified imagers, and the assessment of OCT and FA images at standardized intervals at a masked reading center. Furthermore, there was a broad range of visual acuities and CSTs. Baseline correlations and the relationships between changes in both BCVA and CST from baseline at 24 weeks were assessed, regardless of treatment assignment.

In summary, this analysis assessed the relationships between BCVA and both OCT and FA anatomic biomarkers in patients with RVO-ME using clinical trial data, which involved monitor-verified diagnoses per eligibility criteria, protocol refractions, study-certified imagers, and OCT and FA assessment at a masked reading center. Although there was a moderate correlation between BCVA and CST, both at baseline and for changes from baseline to 24 weeks, there are additional important, clinically relevant relationships between BCVA and both OCT and angiographic features in patients with RVO-ME. At baseline, there was a moderate negative correlation between angiographic leakage and BCVA. At weeks 12 and 24, the mean BCVA in eyes with definitely abnormal (absent) EZ was statistically significantly worse than that in eyes with normal EZ. With respect to changes in macular anatomy and visual function, at weeks 12 and 24, eyes that showed any improvement in central IRF showed a greater improvement in BCVA than eyes that showed no improvement or worsened. In aggregate, the anatomic end points described herein can account for half of the variation in BCVA at baseline, whereas changes in anatomy from baseline can account for nearly 30% of the variation in the change in BCVA from baseline. For clinicians, these findings provide context for assessment and treatment decisions because macular anatomy remains an important treatment criterion in practice. For example, when treatment leads to restoration of macular anatomy, with persistent vision loss in patients with RVO-ME, clinicians should consider other etiologies, such as disruption of anatomic connections, ischemia, and neuropathic dysfunction.

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Abbreviations and Acronyms:

BCVA	best-corrected visual acuity
BRVO	branch retinal vein occlusion
CI	confidence interval
CLS-TA	an investigational formulation of the corticosteroid triamcinolone acetonide, for suprachoroidal injection
CRVO	central retinal vein occlusion
CST	central subfield thickness

EZ	ellipsoid zone
FA	fluorescein angiography
IRF	intraretinal fluid
IVT	intravitreal
ME	macular edema
RVO	retinal vein occlusion
SAPPHIRE	A Randomized, Masked, Controlled Trial to Study the Safety and Efficacy of Suprachoroidal CLS-TA in Conjunction with Intravitreal Aflibercept in Subjects with Retinal Vein Occlusion
SD-OCT	spectral-domain OCT
SC	suprachoroidal
SRF	subretinal fluid
TANZANITE	Safety and Efficacy of Suprachoroidal CLS-TA in Combination with Intravitreal Aflibercept in Subjects with Macular Edema Following Retinal Vein Occlusion
TOPAZ	A Randomized, Masked, Controlled Trial to Study the Safety and Efficacy of Suprachoroidal CLS-TA with an Intravitreal Anti-VEGF in Subjects with Retinal Vein Occlusion.

References

1. Bressler NM, Odia I, Maguire M, et al. Association between change in visual acuity and change in central sub!eld thickness during treatment of diabetic macular edema in participants randomized to aflibercept, bevacizumab, or ranibizumab: a post hoc analysis of the protocol T randomized clinical trial. JAMA Ophthalmol. 2019;137:977–985. [PubMed: 31246237]
2. Diabetic Retinopathy Clinical Research Network. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. Ophthalmology. 2007;114:525–536. [PubMed: 17123615]
3. Ou WC, Brown DM, Payne JF, Wykoff CC. Relationship between visual acuity and retinal thickness during antivascular endothelial growth factor therapy for retinal diseases. Am J Ophthalmol. 2017;180:8–17. [PubMed: 28549848]
4. Ciulla TA, Kapik B, Grewal DS, Ip MS. Visual acuity in retinal vein occlusion, diabetic, and uveitic macular edema: central subfield thickness and ellipsoid zone analysis. Ophthalmol Retina. 2021;5:633–647. [PubMed: 33130256]
5. Scott IU, VanVeldhuisen PC, Oden NL, et al. SCORE Study report 1: baseline associations between central retinal thickness and visual acuity in patients with retinal vein occlusion. Ophthalmology. 2009;116:504–512. [PubMed: 19167078]
6. Scott IU, Ip MS, VanVeldhuisen PC, et al. A randomized trial comparing the efficacy and safety of intravitreal triamcinolone with standard care to treat vision loss associated with macular edema secondary to branch retinal vein occlusion: the Standard Care vs Corticosteroid for Retinal Vein Occlusion (SCORE) study report 6. Arch Ophthalmol. 2009;127:1115–1128. Published correction appears in Arch Ophthalmol. 2009;127:1655. [PubMed: 19752420]

7. Danis RP, Sadda S, Jiao J, et al. Relationship vetween retinal thickness and visual acuity in eyes with retinal vein occlusion treated with dexamethasone implant. Retina. 2016;36:1170–1176. [PubMed: 26655606]

8. Sugar EA, Jabs DA, Altaweel MM, et al. Identifying a clinically meaningful threshold for change in uveitic macular edema evaluated by optical coherence tomography. Am J Ophthalmol. 2011;152:1044–1052. [PubMed: 21861971]

9. Campochiaro PA, Wykoff CC, Brown DM, et al. Suprachoroidal triamcinolone acetonide for retinal vein occlusion: results of the Tanzanite study. Ophthalmol Retina. 2018;2:320–328. [PubMed: 31047241]

10. Ciulla TA, Kapik B, Barakat MR, et al. Optical coherence tomography anatomic and temporal biomarkers in uveitic macular edema. Am J Ophthalmol. 2022;237:310–324. [PubMed: 34740628]

11. Banaee T, Singh RP, Champ K, et al. Ellipsoid zone mapping parameters in retinal venous occlusive disease with associated macular edema. Ophthalmol Retina. 2018;2:836–841. [PubMed: 30221215]

12. Mimouni M, Segev O, Dori D, et al. Disorganization of the retinal inner layers as a predictor of visual acuity in eyes with macular edema secondary to vein occlusion. Am J Ophthalmol. 2017;182:160–167. [PubMed: 28837790]

13. Yiu G, Welch RJ, Wang Y, et al. Spectral-domain OCT predictors of visual outcomes after ranibizumab treatment for macular edema resulting from retinal vein occlusion. Ophthalmol Retina. 2020;4:67–76. [PubMed: 31669329]

14. Campos A, Campos EJ, do Carmo A, et al. Evaluation of markers of outcome in real-world treatment of diabetic macular edema. Eye Vis (Lond). 2018;5:1–10. [PubMed: 29417087]

15. Ehlers JP, Uchida A, Hu M, et al. Higher-order assessment of OCT in diabetic macular edema from the vista study: ellipsoid zone dynamics and the retinal fluid index. Ophthalmol Retina. 2019;3:1056–1066. [PubMed: 31473172]

16. Grewal DS, O'Sullivan ML, Kron M, Jaffe GJ. Association of disorganization of retinal inner layers with visual acuity in eyes with uveitic cystoid macular edema. Am J Ophthalmol. 2017;177:116–125. [PubMed: 28237411]

17. Tortorella P, D'Ambrosio E, Iannetti L, et al. Correlation between visual acuity, inner segment/outer segment junction, and cone outer segment tips line integrity in uveitic macular edema. Biomed Res Int. 2015;2015:853728. [PubMed: 26167505]

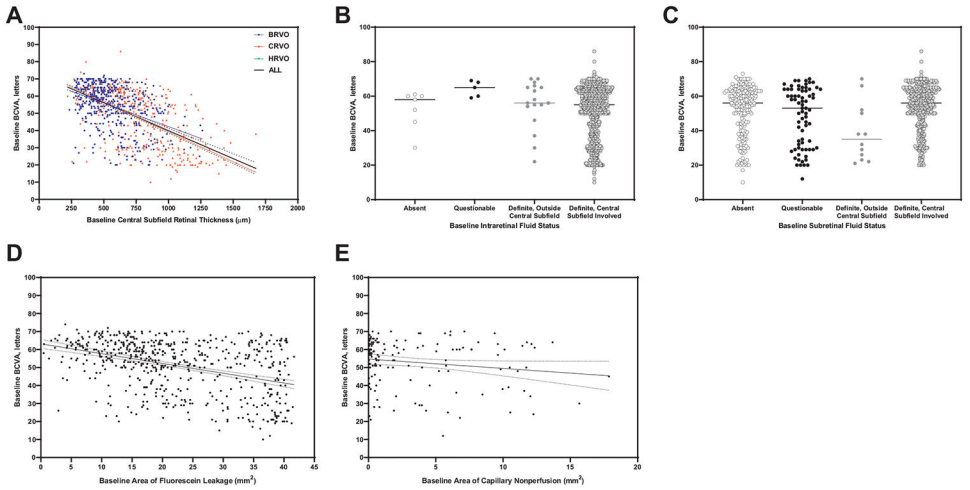

Figure 1.

Scatterplots showing retinal vein occlusion. **A,** Central subfield retinal thickness and ETDRS best-corrected visual acuity (BCVA) at baseline. **B,** Presence and location of intraretinal fluid and ETDRS BCVA at baseline. **C,** Presence and location of subretinal fluid and ETDRS BCVA at baseline. **D,** Area of fluorescein leakage and ETDRS BCVA at baseline. **E,** Area of capillary nonperfusion and ETDRS BCVA at baseline. Linear regression lines (solid) are plotted along with lines (dashed) outlining 95% confidence intervals for mean predicted values.

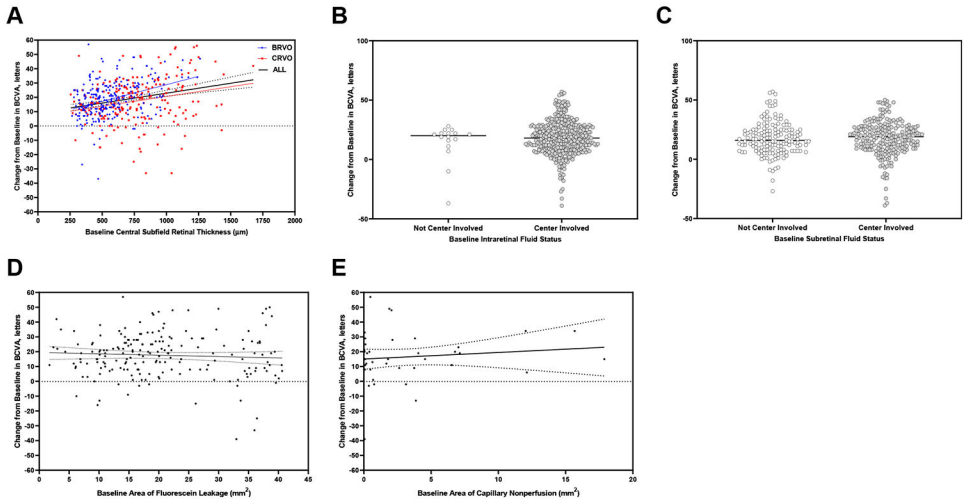

Figure 2.

Scatterplots showing retinal vein occlusion. **A,** Baseline central subfield retinal thickness and change in ETDRS best-corrected visual acuity (BCVA) from baseline to week 24. **B,** Presence and location of intraretinal fluid at baseline and change in ETDRS BCVA from baseline to week 24. **C,** Presence and location of subretinal fluid at baseline and change in ETDRS BCVA from baseline to week 24. **D,** Baseline area of fluorescein leakage and change in ETDRS BCVA from baseline to week 24. **E,** Baseline area of capillary nonperfusion and change in ETDRS BCVA from baseline to week 24. Linear regression lines (solid) are plotted along with lines (dashed) outlining 95% confidence intervals for mean predicted values.

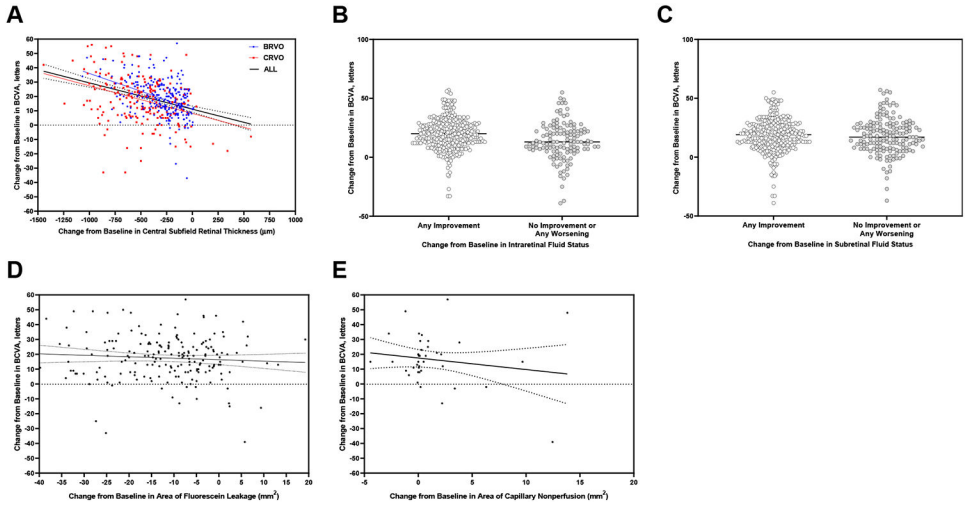

Figure 3.

Scatterplots showing retinal vein occlusion. **A,** Change in central subheld retinal thickness and ETDRS best-corrected visual acuity (BCVA) from baseline to week 24. **B,** Change in the presence and location of intraretinal fluid and ETDRS BCVA from baseline to week 24. **C,** Change in the presence and location of subretinal fluid and ETDRS BCVA from baseline to week 24. **D,** Change in the area of fluorescein leakage and ETDRS BCVA from baseline to week 24. **E,** Change in the area of capillary nonperfusion and ETDRS BCVA from baseline to week 24. Linear regression lines (solid) are plotted along with lines (dashed) outlining 95% confidence intervals for mean predicted values.

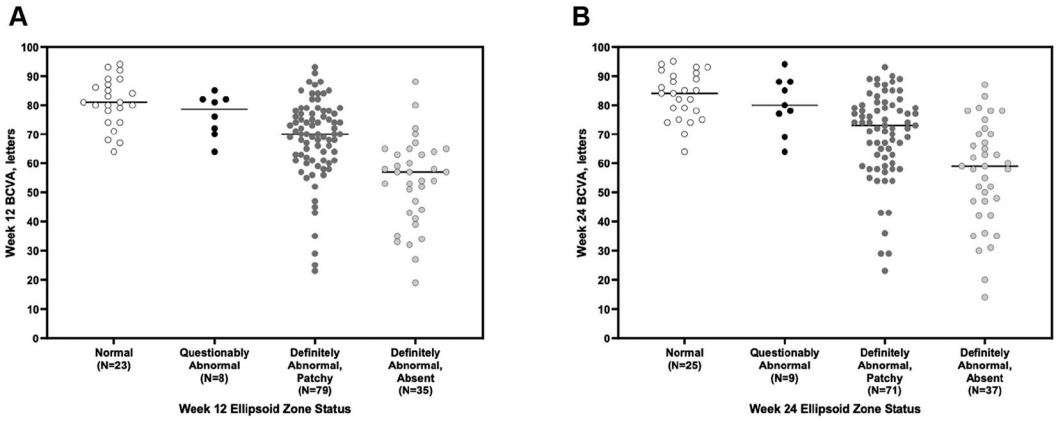

Figure 4.

Scatterplots showing retinal vein occlusion. Ellipsoid zone integrity and ETDRS best-corrected visual acuity (BCVA) at week 12 (**A**) and week 24 (**B**).

Table 1.

Studies Included in the Analysis

Feature	Study		
	TANZANITE	***SAPPHIRE***	***TOPAZ***
ClinicalTrials.gov Identifier	NCT02303184	NCT02980874	NCT03203447
Study title	TANZANITE: Safety and Efficacy of Suprachoroidal CLS-TA in Combination with Intravitreal Aflibercept in Subjects with Macular Edema Following Retinal Vein Occlusion	SAPPHIRE: A Randomized, Masked, Controlled Trial to Study the Safety and Efficacy of Suprachoroidal CLS-TA in Conjunction with Intravitreal Aflibercept in Subjects with Retinal Vein Occlusion	TOPAZ: A Randomized, Masked, Controlled Trial to Study the Safety and Efficacy of Suprachoroidal CLS-TA in Combination with an Intravitreal Anti-VEGF Agent in Subjects with Retinal Vein Occlusion
Disease state	RVO	RVO	RVO
Phase	II	III	III
Planned duration, wks	12	48	48
Study design	Randomized, double-masked, multicenter	Randomized, double-masked, multicenter	Randomized, double-masked, multicenter
Key eligibility features	Diagnosis of treatment-naíve ME associated with RVO; ETDRS BCVA between 20 and 70 letters; CST ≥ 310 μm	Diagnosis of treatment-naíve ME associated with RVO; ETDRS BCVA between 20 and 70 letters; CST ≥ 300 μm	Diagnosis of treatment-naíve ME associated with RVO; ETDRS BCVA between 20 and 70 letters; CST ≥ 300 μm
Treatment(s) [*]	4 mg of suprachoroidal CLS-TA at week 0 with IVT aflibercept or a sham procedure with IVT aflibercept	4 mg of suprachoroidal CLS-TA at weeks 0, 12, and 24 with IVT aflibercept or a sham procedure with IVT aflibercept [†]	4 mg of suprachoroidal CLS-TA at weeks 0, 12, and 24 with IVT anti-VEGF or a sham procedure with IVT anti-VEGF [†]
Number of patients [†]	23 with CLS-TA + IVT aflibercept; 23 with a sham procedure + IVT aflibercept	231 with CLS-TA + IVT aflibercept; 229 with a sham procedure + IVT aflibercept	162 with CLS-TA + IVT anti-VEGF; 163 with a sham procedure + IVT anti-VEGF

BCVA = best-corrected visual acuity; CLS-TA = an investigational formulation of the corticosteroid triamcinolone acetonide, for suprachoroidal injection; CST = central subfield thickness; IVT = intravitreal; ME = macular edema; RVO = retinal vein occlusion.

[*] Patients were eligible for rescue at other visits as determined by predefined criteria.

[†] Three patients in SAPPHIRE (1 CLS-TA + aflibercept and 2 aflibercept) did not have gradable OCT images at baseline. These 3 patients were excluded from this analysis.

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Table 2.

Demographic and Baseline Characteristics

Characteristic	Study			Total
	TANZANITE	*SAPPHIRE*	*TOPAZ*	
No. of participants	46	457	325	828
Mean age (range), yrs	66.3 (37-91)	65.7 (32-93)	63.2 (31-97)	64.7 (31-97)
Women, no. (%)	23 (50.0)	202 (44.2)	152 (46.8)	377 (45.5)
White, no. (%)	38 (82.6)	358 (77.9)	161 (50.2)	557 (67.3)
Phakic, no. (%)	36 (78.3)	377 (81.8)	257 (79.7)	669 (80.8)
Duration of RVO, days				
Mean (range)	34.1 (1-363)	38.0 (1-5851)	25.6 (4-166)	33.0 (1-5851)
Median	11.5	10.0	21.0	15.0
Type of RVO, n (%)				
BRVO	19 (41.3)	248 (54.3)	186 (57.2)	453 (54.7)
CRVO	26 (56.5)	209 (45.7)	139 (42.8)	374 (45.2)
HRVO	1 (2.2)	0	0	1 (0.1)
Perfusion, n (%)				
Ischemic	11 (23.9)	85 (18.6)	37 (11.4)	133 (16.1)
Non-ischemic	35 (76.1)	337 (73.7)	256 (78.8)	628 (75.8)
Unknown	0	35 (7.7)	32 (9.8)	64 (8.1)
Duration of ME, days				
Mean (range)	27.0 (0-240)	33.8 (1-1830)	41.4 (4-1846)	36.9 (1-1846)
Median	18.0	11.0	25.0	18.0
BCVA, mean (range)				
ALL				
ETDRS letters	48.8 (20-80)	50.7 (10-73)	51.9 (20-86)	51.1 (10-86)
Snellen equivalent	20/126 (20/500-20/32)	20/126 (20/800-20/40)	20/100 (20/500-20/20)	20/100 (20/800-20/20)
BRVO	55.6 (31-68)	54.1 (20-73)	54.1 (21-70)	54.2 (20-73)
CRVO	44.5 (20-80)	46.7 (10-70)	48.8 (20-86)	47.3 (10-86)
CST, mean (range), μm				
ALL	729.3 (362-1480)	660.1 (234-1676)	642.0 (220-1527)	656.9 (220-1676)

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Characteristic	Study			Total
	TANZANITE	*SAPPHIRE*	*TOPAZ*	
BRVO	607.0 (406-1029)	574.4 (234-1262)	549.7 (268-1005)	565.6 (234, 1262)
CRVO	811.5 (362-1480)	761.9 (255-1676)	765.5 (220-1527)	766.7 (220-1676)

BCVA = best-corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CST = central subheld thickness; HRVO = hemiretinal vein occlusion; ME = macular edema; RVO = retinal vein occlusion; SAPPHIRE = A Randomized, Masked, Controlled Trial to Study the Safety and Efficacy of Suprachoroidal CLS-TA in Conjunction with Intravitreal Aflibercept in Subjects with Retinal Vein Occlusion; TANZANITE = Safety and Efficacy of Suprachoroidal CLS-TA in Combination with Intravitreal Aflibercept in Subjects with Macular Edema Following Retinal Vein Occlusion; TOPAZ = A Randomized, Masked, Controlled Trial to Study the Safety and Efficacy of Suprachoroidal CLS-TA with an Intravitreal Anti-VEGF in Subjects with Retinal Vein Occlusion

Table 3.

Correlation Analysis Between Best Corrected Visual Acuity and Central Subfield Retinal Thickness

Time Point	BCVA and Central Subfield Retinal Thickness			
	No.	*Pearson Correlation Coefficient (95% CI)*	*P Value* *	*BCVA per 100-μm Absolute Reduction in CST (95% CI)* †
Baseline				
ALL	828	–0.56 (–0.61, –0.51)	<0.001	3.28 (2.96, 3,61)
BRVO	453	–0.42 (–0.49, –0.34)	<0.001	2.75 (2.21, 3.29)
CRVO	374	–0.59 (–0.66, –0.52)	<0.001	3.56 (3.08, 4.03)
	No.	**Pearson Correlation Coefficient (95% CI)**	***P* Value***	**Change in BCVA per 100-μm Absolute Reduction in CST (95% CI)**
Week 12				
ALL				
Baseline CST vs. Change in BCVA	632	0.31 (0.23, 0.38)	<0.001	–0.31 (–0.73, 0.11)‡
Change in CST vs. Change in BCVA	632	–0.35 (–0.42, –0.28)	<0.001	2.45 (1.56, 3.35)§
BRVO				
Baseline CST vs. Change in BCVA	324	0.40 (0.30, 0.49)	<0.001	–1.16 (–1.75, –0.58)‡
Change in CST vs. Change in BCVA	324	–0.44 (–0.52, –0.35)	<0.001	2.62 (1.32, 3.92)§
CRVO				
Baseline CST vs. Change in BCVA	307	0.30 (0.20, 0.40)	<0.001	–0.22 (–0.87, 0.42)‡
Change in CST vs. Change in BCVA	307	–0.34 (–0.44, –0.24)	<0.001	2.22 (0.99, 3.45)§
Week 24				
ALL				
Baseline CST vs. Change in BCVA	455	0.25 (0.16, 0.33)	<0.001	0.20 (–0.36, 0.76)‡
Change in CST vs. Change in BCVA	455	–0.35 (–0.43, –0.27)	<0.001	2.87 (1.89, 3.84)§
BRVO				
Baseline CST vs. Change in BCVA	246	0.38 (0.26, 0.48)	<0.001	–1.03 (–1.78, –0.28)‡

Change in CST vs. Change in BCVA	246	–0.43 (–0.52, –0.32)	<0.001	3.19 (1.35, 5.04)[§]
CRVO				
Baseline CST vs. Change in BCVA	209	0.24 (0.10, 0.36)	<0.001	0.56 (–0.33, 1.45)[‡]
Change in CST vs. Change in BCVA	209	–0.36 (–0.47, –0.24)	<0.001	2.52 (1.28, 3.77)[§]

ALL = includes patients with BRVO, CRVO and HRVO; BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CI = confidence interval; CRVO = central retinal vein occlusion; CST = central subfield retinal thickness; HRVO = hemiretinal vein occlusion.

[*] Test of the null hypothesis that the correlation coefficient is equal to zero. Fisher's z transformation was used in calculating the Pearson coefficient's 95% CI and *P* value.

[†] Based on a multiple linear regression with baseline BCVA as the dependent variable and baseline central subfield retinal thickness and age as the independent variables.

[‡] Based on a multiple linear regression with change from baseline in BCVA as the dependent variable and baseline central subfield retinal thickness, age, and baseline best corrected visual acuity as the independent variables.

[§] Based on a multiple linear regression with change from baseline in BCVA as the dependent variable and change from baseline in central subfield retinal thickness, age, and baseline best corrected visual acuity and central subfield thickness as the independent variables.

Table 4.

Association between BCVA and the Presence and Location of IRF*

	Baseline IRF Status			
Baseline BCVA, Letters	***Absent (1)***	***Questionable (2)***	***Definite, Outside Central Subfield (3)***	***Definite, Central Subfield Involved (4)***
n	7	5	17	783
Mean (SE)	42.2 (4.61)	55.0 (5.44)	45.2 (2.98)	51.2 (0.43)
Difference (95% CI) vs. 1 †		– 12.8 (– 31.1 to 5.5)	– 3.0 (– 17.0 to 11.0)	– 9.0 (– 20.9 to 3.0)
P value vs. 1		0.271	0.946	0.215
Difference (95% CI) vs. 2			9.8 (– 6.1 to 25.7)	3.9 (– 10.2 to 17.9)
P value vs. 2			0.384	0.895
Difference (95% CI) vs. 3				– 6.0 (– 13.7 to 1.8)
P value vs. 3				0.198
	Baseline IRF vs. Wk 12		**Baseline IRF vs. Wk 24**	
Change in BCVA from Baseline, Letters	***Center Not Involved***	***Center Involved***	***Center Not Involved***	***Center Involved***
n	18	557	16	417
Mean (SE)	15.5 (2.64)	17.1 (0.47)	14.4 (3.14)	18.6 (0.60)
Difference (95% CI) ‡		– 1.6 (– 6.8 to 3.7)		– 4.2 (– 10.5 to 2.1)
P value		0.563		0.188
	Change in IRF from Baseline vs. Wk 12		**Change in IRF from Baseline vs. Wk 24**	
Change in BCVA from Baseline, Letters	***Any Improvement***	***No Improvement or Worsening***	***Any Improvement***	***No Improvement or Worsening***
n	463	177	332	131
Mean (SE)	18.3 (0.52)	13.0 (0.83)	20.2 (0.66)	13.3 (1.06)
Difference (95% CI) §		5.2 (3.3–7.2)		7.0 (4.5–9.4)
P value		> 0.001		> 0.001

BCVA = best-corrected visual acuity; CI = confidence interval; IRF = intraretinal fiuid; SE = standard error of the mean.

* Spectral-domian OCT images with reading center grades of being ungradable were excluded from the analysis. Descriptive statistics were derived from the statistical analysis, i.e., least-squared means and standard errors.

[†]Between-group differences, 95% CIs, and *P* values were based on an analysis of covariance model with baseline BCVA as the dependent variable, the baseline IRF grade as the independent variable, and baseline central subfield thickness and age as covariates. The *P* values were adjusted using the Tukey–Kramer method for multiple comparisons.

[‡]Between-group differences, 95% CIs, and *P* values were based on an analysis of covariance model with change in BCVA from baseline as the dependent variable, baseline IRF grade as the independent variable, and baseline BCVA, baseline central subfield thickness, and age as covariates.

[§]Between-group differences, 95% CIs, and *P* values were based on an analysis of covariance model with change in BCVA from baseline as the dependent variable, change in IRF from baseline as the independent variable, and baseline BCVA, baseline central subfield thickness, and age as covariates.

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Table 5.

Association between BCVA and the Presence and Location of SRF*

	Baseline SRF			
Baseline BCVA, Letters	***Absent (1)***	***Questionable (2)***	***Definite, Outside Central Subfield (3)***	***Definite, Central Subfield Involved (4)***
n	210	73	12	449
Mean (SE)	48.7 (0.83)	48.9 (1.37)	41.1 (3.38)	54.9 (0.56)
Difference (95% CI) vs. 1†		– 0.1 (– 4.3 to 4.0)	7.6 (– 1.4 to 16.6)	– 6.1 (– 8.8 to – 3.5)
P value vs. 1		1.000	0.132	> 0.001
Difference (95% CI) vs. 2			7.7 (– 1.7 to 17.1)	– 6.0 (– 9.8 to – 2.2)
P value vs. 2			0.149	> 0.001
Difference (95% CI) vs. 3				– 13.7 (– 22.5 to – 4.9)
P value vs. 3				> 0.001
Change in BCVA from Baseline, Letters	**Baseline SRF vs. Wk 12**		**Baseline SRF vs. Wk 24**	
	Center Not Involved	***Center Involved***	***Center Not Involved***	***Center Involved***
n	223	304	157	231
Mean (SE)	15.8 (0.76)	16.9 (0.64)	17.1 (1.01)	18.2 (0.82)
Difference (95% CI)‡		– 1.2 (– 3.2 to 0.8)		– 1.1 (– 3.7 to 1.6)
P value		0.250		0.421
	Change in SRF from Baseline vs. Wk 12		**Change in SRF from Baseline vs. Wk 24**	
Change in BCVA from Baseline, Letters	***Any Improvement***	***No Improvement or Worsening***	***Any Improvement***	***No Improvement or Worsening***
n	407	233	298	164
Mean (SE)	17.5 (0.56)	15.7 (0.75)	19.1 (0.73)	16.8 (0.98)
Difference (95% CI)§		1.8 (– 0.1 to 3.7)		2.3 (– 0.2 to 4.7)
P value		0.060		0.069

BCVA = best-corrected visual acuity; CI = confidence interval; SE = standard error of the mean; SRF = subretinal fiuid.

*Spectral-domain OCT images with reading center grades of being ungradable were excluded from the analysis. Descriptive statistics were derived from the statistical analysis, i.e., least-squared mean and standard errors.

[†]Between-group differences, 95% CIs, and *P* values were based on an analysis of covariance model with baseline BCVA as the dependent variable, baseline SRF grade as the independent variable, and baseline central subfield thickness and age as covariates. The *P* values are adjusted using the Tukey–Kramer method for multiple comparisons.

[‡]Between-group differences, 95% CIs, and *P* values were based on an analysis of covariance model with change in BCVA from baseline as the dependent variable, baseline SRF grade as the independent variable, and baseline BCVA, baseline central subfield thickness, and age as covariates.

[§]Between-group differences, 95% CIs, and *P* values were based on an analysis of covariance model with change in BCVA from baseline as the dependent variable, change in SRF from baseline as the independent variable, and baseline BCVA, baseline central subfield thickness, and age as covariates.

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Table 6.

Correlation Analysis between BCVA and FA Outcomes

	BCVA and FA Outcomes			
FA Outcome	***n***	***Pearson Correlation Coefficient (95% CI)***	**P *Value*** [*]	***BCVA per 10-mm² Absolute Reduction in FA Outcome (95% CI)*** [†]
Baseline [‡]				
Fluorescein leakage	578	– 0.41 (– 0.47 to – 0.34)	< 0.001	1.98 (0.93–3.03)
Capillary nonperfusion	135	– 0.16 (– 0.32 to 0.01)	0.060	2.87 (– 1.48 to 7.22)
	n	**Pearson Correlation Coefficient (95% CI)**	***P* Value**	**Change in BCVA per 10-mm² Reduction in FA Outcome (95% CI)**
Wk 24 [§]				
Fluorescein leakage	190	– 0.06 (– 0.20 to 0.08)	0.384	3.64 (1.61–5.66) [‖]
Baseline FL vs. change in BCVA	190	– 0.07 (– 0.21 to 0.07)	0.323	– 0.16 (– 1.87 to 1.55) [¶]
Change in FL vs. change in BCVA				
Capillary nonperfusion	39	0.12 (– 0.21 to 0.42)	0.482	1.43 (– 7.99 to 10.85) [‖]
Baseline CN vs. change in BCVA	39	– 0.17 (– 0.46 to 0.16)	0.315	– 6.48 (– 18.5 to 5.53) [¶]
Change in CN vs. change in BCVA				

BCVA = best-corrected visual acuity; CI = confidence interval; CN = capillary nonperfusion; FA = fluorescein angiography; FL = fluorescein leakage.

[*] Test of null hypothesis, where the correlation coefficient is equal to zero. Fisher *z* transformation was used for calculating the Pearson coefficient, 95% CI, and *P* value.

[†] Based on multiple linear regression with baseline BCVA as the dependent variable and baseline FA outcome, age, and baseline central subfield thickness as independent variables.

[‡] Baseline includes FA outcomes from the TANZANITE, SAPPHIRE, and TOPAZ trials.

[§] Week 24 includes FA outcomes from the SAPPHIRE and TOPAZ trials.

[‖] Based on multiple linear regression with change in BCVA from baseline as the dependent variable and baseline FA outcome, age, and baseline BCVA and central subfield thickness as independent variables.

[¶] Based on multiple linear regression with change in BCVA from baseline as the dependent variable and change in FA outcome from baseline, age, and baseline BCVA and central subfield thickness as independent variables.

Table 7.

Association between BCVA and EZ Integrity[*,†]

BCVA, Letters	EZ Status			
At Wk 12	***Normal (1)***	***Questionably Abnormal (2)***	***Definitely Abnormal (Patchy) (3)***	***Definitely Abnormal (Absent) (4)***
n	23	8	79	35
Mean (SE)	74.4 (2.52)	73.5 (4.04)	68.5 (1.28)	58.0 (2.02)
Difference (95% CI) vs. 1		0.8 (– 11.4 to 13.0)	5.8 (– 1.6 to 13.2)	16.4 (7.6–25.2)
P value vs. 1		0.998	0.177	> 0.001
Difference (95% CI) vs. 2			5.0 (– 6.1 to 16.0)	15.5 (3.7–27.4)
P value vs. 2			0.645	0.005
Difference (95% CI) vs. 3				10.6 (4.3–16.8)
P value vs. 3				> 0.001
At Wk 24				
n	25	9	71	37
Mean (SE)	77.6 (2.57)	72.2 (4.25)	70.5 (1.47)	60.6 (2.11)
Difference (95% CI) vs. 1		5.4 (– 7.2 to 17.9)	7.2 (– 0.7 to 15.0)	17.0 (8.1–25.9)
P value vs. 1		0.683	0.085	> 0.001
Difference (95% CI) vs. 2			1.8 (– 9.9 to 13.5)	11.6 (– 1.1 to 24.3)
P value vs. 2			0.979	0.086
Difference (95% CI) vs. 3				9.8 (3.2–16.5)
P value vs. 3				0.001

BCVA = best-corrected visual acuity; CI = confidence interval; EZ = ellipsoid zone; SE = standard error of the mean.

[*] Spectral-domain OCT images with reading center grades of being ungradable were excluded from the analysis. Descriptive statistics were derived from the statistical analysis, i.e., the least-squares means and standard errors.

[†] Between-group differences, 95% CIs, and *P* values were based on an analysis of covariance model with BCVA letter score as the dependent variable, EZ grade as the independent variable, and baseline central subfield thickness and age as covariates. The *P* values were adjusted using the Tukey–Kramer method for multiple comparisons.

Table 8.

Coefficients of Determination from BCVA with OCT and Fluorescein Angiography Anatomy at Baseline and Week 24 *

	Baseline BCVA and Anatomy †		Change in BCVA and Anatomy from Baseline †	
Anatomy	***Model***	**r^2, %** §	***Model***	**r^2, %** §
Presence and location of intraretinal fluid	ANCOVA	33.62	ANCOVA	29.70
	ANOVA	0.60	ANOVA	3.90
Presence and location of subretinal fluid	ANCOVA	31.32	ANCOVA	25.34
	ANOVA	3.00	ANOVA	0.03
Central subfield retinal thickness	Multiple linear regression	33.21	Multiple linear regression	30.07
	Simple linear regression	31.66	Simple linear regression	12.25
Fluorescein leakage	Multiple linear regression	34.53	Multiple linear regression	27.82
	Simple linear regression	16.76	Simple linear regression	0.50
Capillary nonperfusion	Multiple linear regression	39.31	Multiple linear regression	46.60
	Simple linear regression	2.64	Simple linear regression	2.76
All outcomes	ANCOVA	49.81	ANCOVA	27.89

ANOVA = analysis of variance; ANCOVA = analysis of covariance; BCVA = best-corrected visual acuity.

* For the baseline intraretinal fluid and subretinal fluid data via OCT, the analysis of covariance model included baseline BCVA as the dependent variable, baseline OCT anatomy as the independent variable, and baseline central subfield thickness (CST) and age as covariates. The analysis of variance model included baseline BCVA as the dependent variable and baseline OCT anatomy as the independent variable. For week 24, intraretinal fluid and subretinal fluid data, the analysis of covariance model included change in BCVA from baseline as the dependent variable, change in OCT anatomy from baseline as the independent variable, and baseline BCVA, baseline CST, and age as covariates. The analysis of variance model included change in BCVA from baseline as the dependent variable and change in OCT anatomy from baseline as the independent variable. For baseline fluorescein leakage and capillary nonperfusion via fluorescein angiography (FA), the multiple linear regression included baseline BCVA as the dependent variable and baseline FA anatomy, age, and baseline CST as independent variables. The simple linear regression included baseline BCVA as the dependent variable and baseline FA anatomy as the independent variable. For fluorescein leakage and capillary nonperfusion at week 24, the multiple linear regression included change in BCVA from baseline as the dependent variable, and baseline BCVA, baseline CST, age, and change in FA anatomy from baseline as independent variables. The simple linear regression included change in BCVA from baseline as the dependent variable and change in FA anatomy from baseline as the independent variable. For all outcomes, the modeling of baseline BCVA consisted of the analysis of covariance model with baseline BCVA as the dependent variable, and baseline CST intraretinal fluid, subretinal fluid fluorescein leakage, and capillary nonperfusion, and age as independent variables and covariates. For all outcomes, the modeling of change in BCVA from baseline to week 24 consisted of the analysis of covariance model with change in BCVA from baseline toweek 24 as the dependent variable, and baseline BCVA, central subfield thickness (CST), intraretinal fluid, subretinal fluid, fluorescein leakage*, capillary nonperfusion and age as independent variables and covariates.

† Includes OCT and FA outcomes from the TANZANITE, SAPPHIRE, and TOPAZ trials.

‡ Includes OCT and FA outcomes from the SAPPHIRE and TOPAZ trials.

§ The coefficient of determination (r^2) is the proportion of variance that is predicted from the independent variables.